

On Keiding's Equation and its relation to differential equations about prevalence and incidence in chronic disease epidemiology

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Abstract

We study the relation between the age-specific prevalence, incidence and mortality in an illness-death model consisting of the three states *Healthy*, *Ill*, *Dead*. The dependency on three different time scales (age, calendar time, disease duration) is considered. It is shown that Keiding's equation published in 1991 is a generalisation of the solution of Brunet and Struchiner's partial differential equation from 1999. In a special case, we propose a particularly simple estimate of the incidence from prevalence data.

1 Background

Keiding reviewed the relations between the incidence and prevalence of a chronic disease based on an illness-death model [7]. The illness-death model consists of the three states *Healthy*, *Ill* and *Dead* (Figure 1). The transition rates i , m_0 , and m_1 between the states may depend on the time scales calendar time (t), age (a), and the rate m_1 may additionally depend on the duration of the disease (d). As we are dealing with chronic diseases, there is no transition from the state *Ill* to *Healthy*. Let $S(t, a)$ denote the number of persons aged a , $a \geq 0$ at time t in the state *Healthy*. Similarly, $C(t, a, d)$ denotes the number of persons aged a at t who are diseased for d , $d \geq 0$ time units. The notation is chosen for historical reasons, S and C stand for susceptibles and cases, respectively.

In epidemiology, it is common to consider the age-specific prevalence

$$p(t, a) = \frac{C^*(t, a)}{C^*(t, a) + S(t, a)},$$

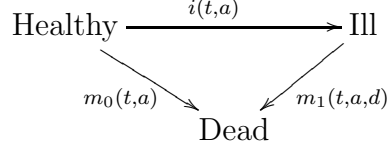


Figure 1: Illness-death model. The transition rates i and m_0 depend on calendar time t and age a . The rate m_1 additionally depends on the duration d .

where $C^*(t, a) = \int_0^a C(t, a, \delta) d\delta$ denotes the number of diseased persons aged a at time t , irrespective of the duration d . Keiding gave following expression for the prevalence odds [7, p. 379]:

$$(1) \quad \frac{p(t, a)}{1 - p(t, a)} = \frac{\int_0^a \mathcal{M}_{t,a}(y) i(t - a + y, y) e^{-\int_y^a m_1(t - a + \tau, \tau, \tau - y) d\tau} dy}{\mathcal{M}_{t,a}(a)}$$

with

$$\mathcal{M}_{t,a}(y) = \exp \left(- \int_0^y m_0(t - a + \tau, \tau) + i(t - a + \tau, \tau) d\tau \right).$$

From Equation (1) the following Proposition can be deduced.

Proposition 1. *For the age-specific prevalence $p(t, a)$ it holds*

$$(2) \quad p(t, a) = \frac{\int_0^a i(t - \delta, a - \delta) \mathcal{M}_{t,a}(a - \delta) e^{-M_1(t, a, \delta)} d\delta}{\mathcal{M}_{t,a}(a) + \int_0^a i(t - \delta, a - \delta) \mathcal{M}_{t,a}(a - \delta) e^{-M_1(t, a, \delta)} d\delta},$$

where

$$M_1(t, a, d) := \int_0^d m_1(t - d + \tau, a - d + \tau, \tau) d\tau.$$

Proof. Solving Equation (1) for $p(t, a)$ and re-parametrising the path of integration yields Eq. (2). \square

Keiding has not presented a proof of Equation (1). In this article, we will give a proof and relate Equation 2 to two partial differential equations (PDEs) published a few years after Keiding's pivotal work in 1991.

2 Partial differential equations

In this section, we will formulate PDEs for $S(t, a)$ and $C(t, a, d)$ based on the model in Figure 1. The only assumptions are

- All newborns are disease-free at time of birth (i.e., $C^*(t, 0) = 0$ for all t .)
- There is no migration into or from the states *Healthy* and *Ill*.
- The rates i, m_0 and m_1 are smooth, i.e. partially differentiable with continuous derivatives.

For the number S of susceptibles we obtain following PDE:

$$(3) \quad \begin{aligned} (\partial_t + \partial_a) S(t, a) &= -(m_0(t, a) + i(t, a)) S(t, a) \\ S(t - a, 0) &= S_0(t - a). \end{aligned}$$

Here $S_0(t - a) = S(t - a, 0)$ denotes the number of (healthy) newborns at time $t - a$. The notation ∂_x means the partial derivative for x , $x \in \{t, a\}$. Equation (3) together with the initial condition $S_0(t - a) = S(t - a, 0)$ is a Cauchy problem which has a unique solution (the rates m_0 and i are smooth) [9]. This solution of the Cauchy problem is given in Eq. (4).

$$(4) \quad S(t, a) = S_0(t - a) \exp \left(- \int_0^a m_0(t - a + \tau, \tau) + i(t - a + \tau, \tau) d\tau \right).$$

The calculation of the number C of cases will be a bit more difficult, because at any time t and at any age a the current disease duration d plays an important role. As there is no migration, the number $C(t, a, d)$ is described by the following equations:

$$\begin{aligned} C(t, a, d) &= C(t - d, a - d, 0) \exp \left(- \int_0^d m_1(t - d + \tau, a - d + \tau, \tau) d\tau \right) \\ &= i(t - d, a - d) S(t - d, a - d) e^{-\int_0^d m_1(t - d + \tau, a - d + \tau, \tau) d\tau}. \end{aligned}$$

$C(t, a, d)$ is a solution of another Cauchy problem. The associated PDE is

$$(\partial_t + \partial_a + \partial_d) C(t, a, d) = -C(t, a, d) m_1(t, a, d),$$

and the initial condition is $C(t, a, 0) = i(t, a) S(t, a)$ for all t, a .

Proof. It holds

$$\begin{aligned}\partial_x C(t, a, d) = & \partial_x i(t-d, a-d) S(t-d, a-d) \exp \{-M_1(t, a, d)\} \\ & + i(t-d, a-d) \partial_x S(t-d, a-d) \exp \{-M_1(t, a, d)\} \\ & - i(t-d, a-d) S(t-d, a-d) \exp \{-M_1(t, a, d)\} \times \\ & \partial_x M_1(t, a, d)\end{aligned}$$

and

$$\begin{aligned}\partial_d C(t, a, d) = & -(\partial_t + \partial_a) i(t-d, a-d) S(t-d, a-d) \exp \{-M_1(t, a, d)\} \\ & - i(t-d, a-d) (\partial_t + \partial_a) S(t-d, a-d) \exp \{-M_1(t, a, d)\} \\ & - i(t-d, a-d) S(t-d, a-d) \exp \{-M_1(t, a, d)\} \times \\ & \partial_d M_1(t, a, d).\end{aligned}$$

This implies

$$(\partial_t + \partial_a + \partial_d) C(t, a, d) = -C(t, a, d)(\partial_t + \partial_a + \partial_d) M_1(t, a, d).$$

For $x \in \{t, a\}$ it is

$$\partial_x M_1(t, a, d) = \int_0^d \partial_x m_1(t-d+\tau, a-d+\tau, \tau) d\tau.$$

Furthermore, we find that

$$\partial_d M_1(t, a, d) = - \int_0^d (\partial_t + \partial_a) m_1(t-d+\tau, a-d+\tau, \tau) d\tau + m_1(t, a, d).$$

With the smoothness constraint, this proves that $C(t, a, d)$ is the unique solution of the Cauchy problem. \square

We are interested in the overall number $C^*(t, a)$:

$$\begin{aligned}C^*(t, a) &= \int_0^a C(t, a, \delta) d\delta \\ (5) \quad &= \int_0^a i(t-\delta, a-\delta) S(t-\delta, a-\delta) e^{-\int_0^\delta m_1(t-\delta+\tau, a-\delta+\tau, \tau) d\tau} d\delta\end{aligned}$$

By inserting (4) and (5) into the definition of $p(t, a)$, we obtain Equation (2). As described above, Equation (2) be transformed into Equation (1), which proves Keiding's Equation.

The advantage of the Equations (2) and (1) is that for given incidence $i(t, a)$ and mortality rates $m_0(t, a)$ and $m_1(t, a, d)$, the age-specific prevalence can be calculated for all times t and ages $a \geq 0$. By this, we may estimate the impact of health related interventions with an appropriate treatment of the involved time scales. Unfortunately, the theory suggested by Keiding has rarely been used in epidemiology, public health, or health economics. For instance, instead of treating time as a continuous variable, discrete time steps are preferred, which may impose a considerable discretisation error (for an example of a discretisation error of more than 100%, see [1]). In the article [5], the effect of a health related intervention is estimated by treating time continuously.

As a byproduct from Equation (2) we may conclude:

Remark 1. *The prevalence $p(t, a)$ is independent from the number of newborns S_0 .*

3 Independence from the duration of the disease

In case the mortality m_1 of the diseased persons is independent from the duration d , the number of cases $C^*(t, a)$ is a solution of the following PDE:

$$(6) \quad (\partial_t + \partial_a) \gamma(t, a) = -m_1(t, a) \gamma(t, a) + i(t, a) S(t, a).$$

Proof. Together with the initial condition $\gamma(t - a, 0) = 0$ the PDE (6) has

the solution

$$\begin{aligned}
\gamma(t, a) &= e^{-\int_0^a m_1(t-a+\alpha, \alpha) d\alpha} \left\{ \gamma(t-a, 0) + \right. \\
&\quad \left. \int_0^a i(t-a+\alpha, \alpha) S(t-a+\alpha, \alpha) e^{\int_0^\alpha m_1(t-a+\tau, \tau) d\tau} d\alpha \right\} \\
&= \int_0^a i(t-a+\alpha, \alpha) S(t-a+\alpha, \alpha) e^{-\int_\alpha^a m_1(t-a+\tau, \tau) d\tau} d\alpha \\
&= \int_0^a i(t-\delta, a-\delta) S(t-\delta, a-\delta) e^{-\int_{a-\delta}^a m_1(t-a+\tau, \tau) d\tau} d\delta \\
&= \int_0^a i(t-\delta, a-\delta) S(t-\delta, a-\delta) e^{-\int_0^\delta m_1(t-\delta+\tau, a-\delta+\tau) d\tau} d\delta.
\end{aligned}$$

By comparison with Eq. (5) we see that $C^*(t, a)$ is the solution of the PDE. \square

If we insert (3) and (6) into the definition of $p(t, a)$, we may deduce following PDE [1]:

$$(7) \quad (\partial_t + \partial_a) p = (1 - p) (i - p(m_1 - m_0)).$$

Similarly, we obtain following PDE for the prevalence odds $\pi(t, a) = \frac{p(t, a)}{1-p(t, a)}$ of Brunet and Struchiner [6], which is equivalent to Eq. (7):

$$(8) \quad (\partial_t + \partial_a) \pi = i - \pi(m_1 - m_0 - i).$$

In contrast to the PDE (7), the PDE (8) has the advantage of being linear. Thus, its solution is straightforward and allows a handy simplification of Eq. (2) (see [3, Eq. (1)]).

We conclude this section with the observation that Keiding's Equation (1) is a generalisation of the solution of both PDEs (7) and (8).

4 Incidence being independent from calendar time

An important application of the theory in epidemiology is the question if incidence rate can be recovered from observed prevalence data. This question

has already been mentioned in 1934 [8] and has been studied in [4] with test data. Now it is shown that in the special case of incidence being independent from calendar time $i(t, a) = i(a)$ the dependence of m_1 on the duration d does not have to be known to estimate the incidence. This has the advantage that a possible duration dependency in m_1 may be unknown.

Starting from (4) we find

$$\begin{aligned} I(t, a) &:= \int_0^a i(t - a + \tau, \tau) d\tau = \ln \frac{S_0(t - a)}{S(t, a)} - M_0(t, a) \\ &= \ln S_0(t - a) - \ln S(t, a) - M_0(t, a) \\ &= \ln S_0(t - a) - \ln(1 - p(t, a)) - \ln N(t, a) - M_0(t, a) \end{aligned}$$

with

$$M_0(t, a) := \int_0^a m_0(t - a + \tau, \tau) d\tau.$$

The number $N(t, a)$ denotes the amount of persons aged a at t who are alive ($N = S + C$.) If i is independent from t , it holds

$$\partial_a I(t, a) = i(a) \quad \text{for all } t.$$

Hence, we may deduce following representation of the age-specific incidence:

$$(9) \quad i(a) = \partial_a \left(\ln S_0(t - a) - \ln(1 - p(t, a)) - \ln N(t, a) - M_0(t, a) \right).$$

This is an amazing result, because the occurring variables S_0 and N are well known from demography. Assumed that the mortality m_0 can also be surveyed, the possibly complex $m_1(t, a, d)$ does not have to be known for an estimate of the incidence in case of a given age-specific prevalence $p(t, a)$.

Remark 2. *Many epidemiological studies examine the mortality m_1 of the diseased instead of the mortality m_0 of the non-diseased. Equation (9) suggests a paradoxical study design: Instead of following up on mortality of the diseased persons, the healthy persons are of primary interest.*

5 Examples

5.1 General case

In this subsection the age-specific prevalence $p(t, a)$ for a hypothetical chronic disease is calculated using Equation (2). We assume that t, a and d are

counted in units “years” with $t, a, d \geq 0$. Mortality m_0 is assumed to be of Gompertz-Makeham type,

$$m_0(t, a) = \exp(-10.7 + 0.1 a) (1 - 0.002)^t,$$

and the incidence is given by

$$(10) \quad i(t, a) = \frac{(a-30)_+}{3000} (1 - 0.003)^t.$$

The mortality m_1 of the diseased is assumed to be the product of m_0 and relative mortality $R(d) = (0.2 d - 1)^2 + 1$:

$$m_1(t, a, d) = R(d) m_0(t, a).$$

The integrals \mathcal{M} and M_1 are calculated analytically, which is possible here. The integral from 0 to a in the numerator and denominator in (2) are calculated by Romberg’s rule, which allows an a-priori prescribed accuracy.

Figure 2 shows the resulting age-specific prevalences at $t = 0, 50$, and 100 (in years). The three age profiles have a similar qualitative behaviour: After onset of the disease for $a \geq 30$, the prevalence increases sharply with age and until the seventh decade of life. All three curves reach their maximum at the age of about 80 (years) and then decrease slightly.

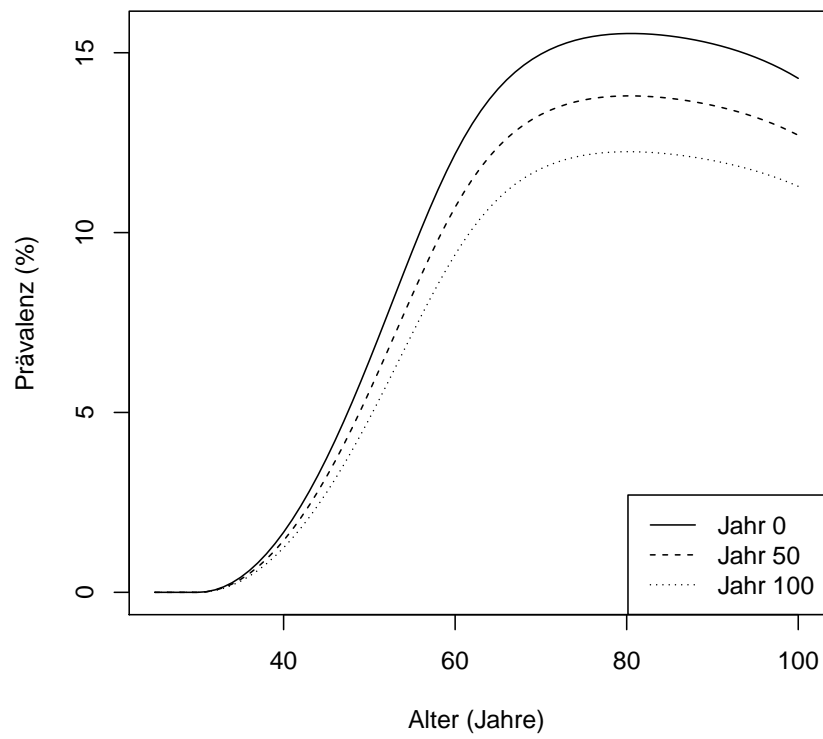


Figure 2: Age-specific prevalences in the example in the years $t = 0, 50$, and 100.

5.2 Time-independent incidence

If we leave out the term $(1 - 0.003)^t$ in Eq. (10), we can estimate $i = i(a)$ from p surveyed in year $t = 100$ via Eq. (9). The partial derivative ∂_a has been approximated by a finite difference. Figure 3 show the results. Visually, there is a nearly perfect agreement between the theoretical and the estimated incidence.

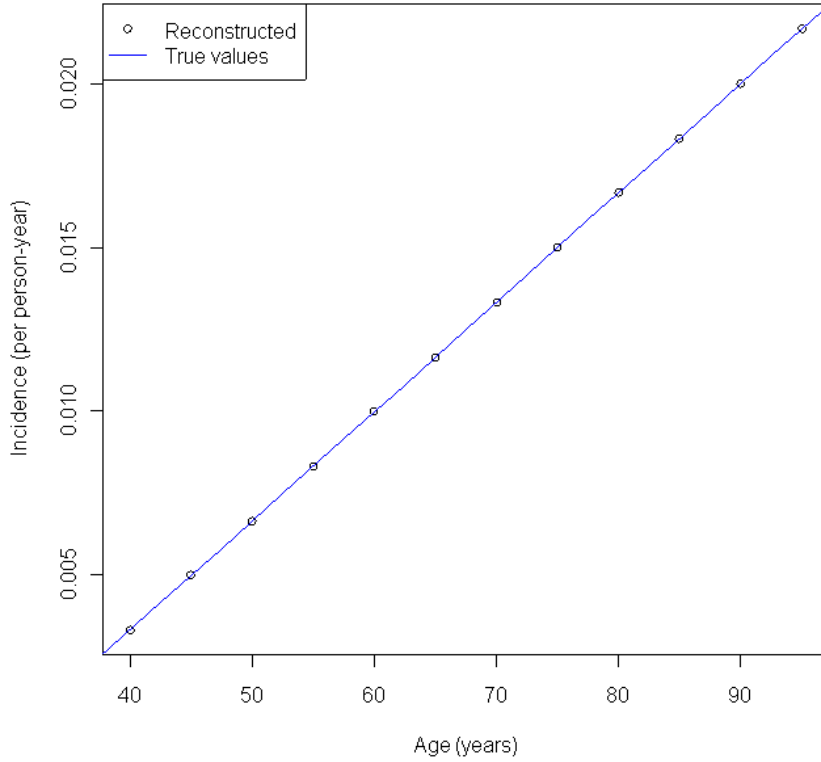


Figure 3: Age-specific incidence in year $t = 100$. The solid line shows the theoretical incidence rate $i(a) = \frac{(a-30)_+}{3000}$. The points represent the estimated values using Equation (9).

Additionally, we set up a population with a birth rate of 5000 persons per year in 60 consecutive years $(0, \dots, 59)$. Events in the illness-death model (diagnosis, death with or without the disease) are simulated by a discrete event simulation as described in [2]. In the year $t = 100$, we mimic a cross-section to estimate the prevalence $p(100, a)$. As above, the incidence is estimated by Eq. (9) and approximating ∂_a by a finite difference. Figure 4 shows the

results. In contrast to Figure 3, the incidence cannot be estimated exactly with is due to the random error in the prevalence $p(100, a)$.

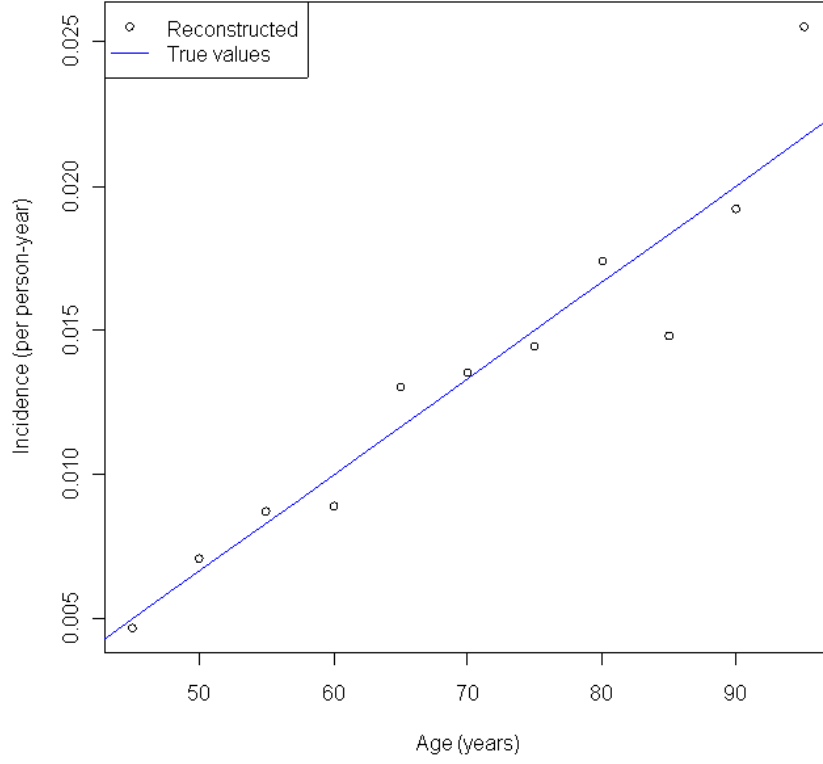


Figure 4: Age-specific incidence in year $t = 100$. The solid line shows the theoretical incidence rate $i(a) = \frac{(a-30)_+}{3000}$. The points represent the estimated values using Equation (9) and the simulated prevalence.

6 Conclusion

This article combines the results of Keiding [7], Brunet and Struchiner [6], and Brinks and Landwehr [1, 3]. We have found that Keiding gave an analytical expression for the age-specific prevalence in the most general case of the illness-death model, i.e. with involvement of all time scales (age, calendar time, and duration). Keiding presented this expression eight years before Brunet and Struchiner published their linear partial differential equation without duration dependency. Brinks and Landwehr extend the work by Keiding and Brunet and Struchiner by allowing migration and remission [1]. Even in the case with duration dependency, the age-specific prevalence can be related to the transition rates in the illness-death model by a scalar partial differential equation. Details can be found in [4].

In addition, we have proposed a new way of estimating the incidence from a cross-sectional prevalence study where it is not necessary to survey the possibly complex duration dependency of m_1 . In this *paradoxical study design*, the mortality of the healthy (m_0) needs to be known instead of the mortality of the diseased (m_1). The proposed method was demonstrated by an example of a hypothetical chronic disease.

References

- [1] BRINKS R, LANDWEHR S (2014) Age- and time-dependent model of the prevalence of non-communicable diseases and application to dementia in Germany, *Theor Popul Biol* 92:62–68.
- [2] BRINKS R, LANDWEHR S, FISCHER-BETZ R, SCHNEIDER M, GIANI G (2014) Lexis diagram and illness-death Model: Simulating populations in chronic disease epidemiology. *PLoS ONE* 9(9): e106043
- [3] BRINKS R, LANDWEHR S (2015) Change rates and prevalence of a dichotomous Variable: Simulations and applications, *PLoS ONE* 10(3): e0118955
- [4] BRINKS R, LANDWEHR S (2015) A new relation between prevalence and incidence of a chronic disease, *Math Med Biol* 32(4): 425–435
- [5] BRINKS R, HOYER A, KUSS O, RATHMANN W (2015) Projected effect of increased active travel in German urban regions on the risk of type 2 diabetes, *PLoS ONE* 10(4): e0122145.

- [6] BRUNET RC, STRUCHINER CJ (1999) A non-parametric method for the reconstruction of age- and time-dependent incidence from the prevalence data of irreversible diseases with differential mortality, *Theor Popul Bio* 56(1): 76–90.
- [7] KEIDING N (1991) Age-specific incidence and prevalence: a statistical perspective. *J Roy Stat Soc A*, 154:371–412.
- [8] MUENCH H (1934). Derivation of rates from summation data by the catalytic curve. *Journal Americ Stat Assoc* 29(185):25-38.
- [9] POLYANIN AD, ZAITSEV VF, MOUSSIAUX A (2000). *Handbook of first order partial differential equations*, Taylor & Francis, London.